



Inhibition of human Ether-à-go-go related gene 1 leads to radiation sensitization in glioblastoma

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Aspiring Scientists and Physicians Program

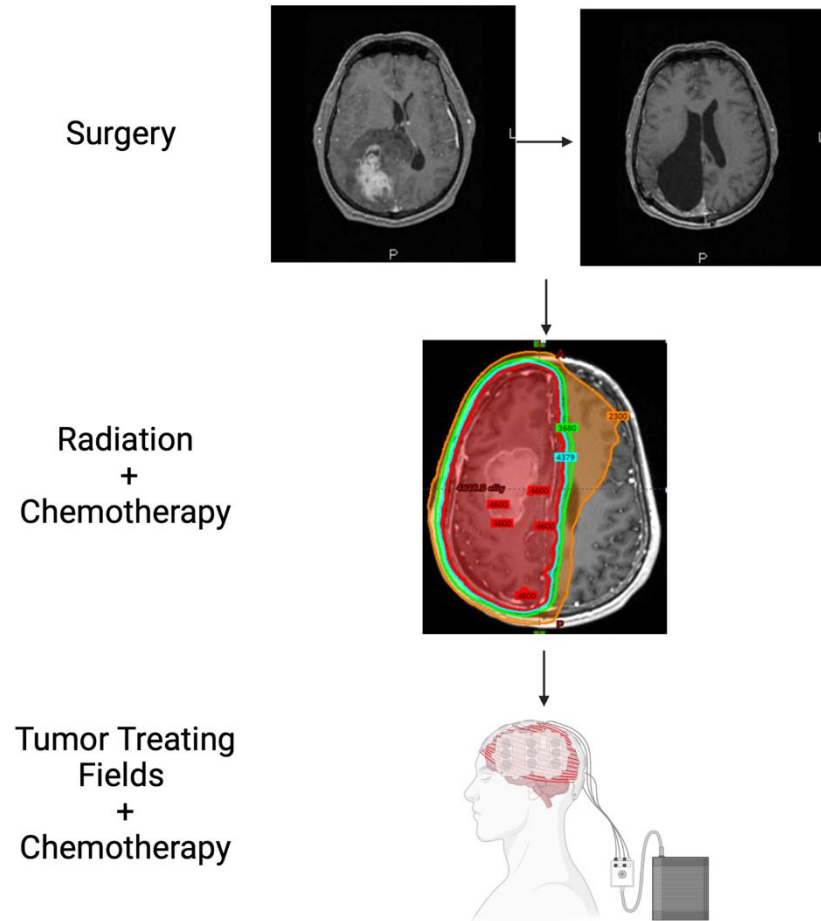
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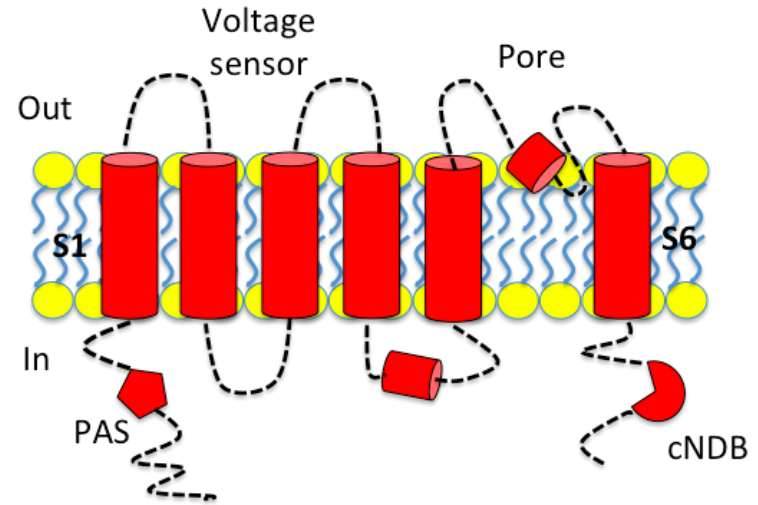
BACKGROUND

- Glioblastoma (GBM) is the most aggressive and malignant primary brain tumor. It has a median survival of less than 2 years despite standard of care.
- Poor outcomes are thought to be driven by tumor recurrences, often happens in the high dose radiation treatment field.
- Research has demonstrated that tumor heterogeneity exists with tumor cells being able to shift from less aggressive (proneural) to more aggressive stem-like (mesenchymal) states.
- Radiation therapy, among other factors, has been shown to transform cells into more aggressive mesenchymal states.



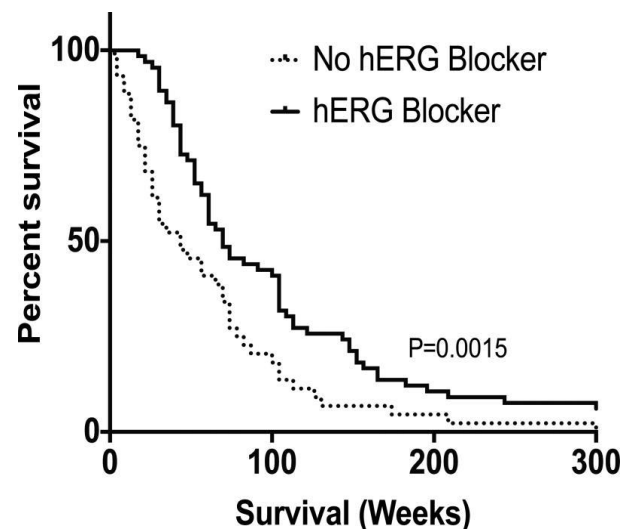
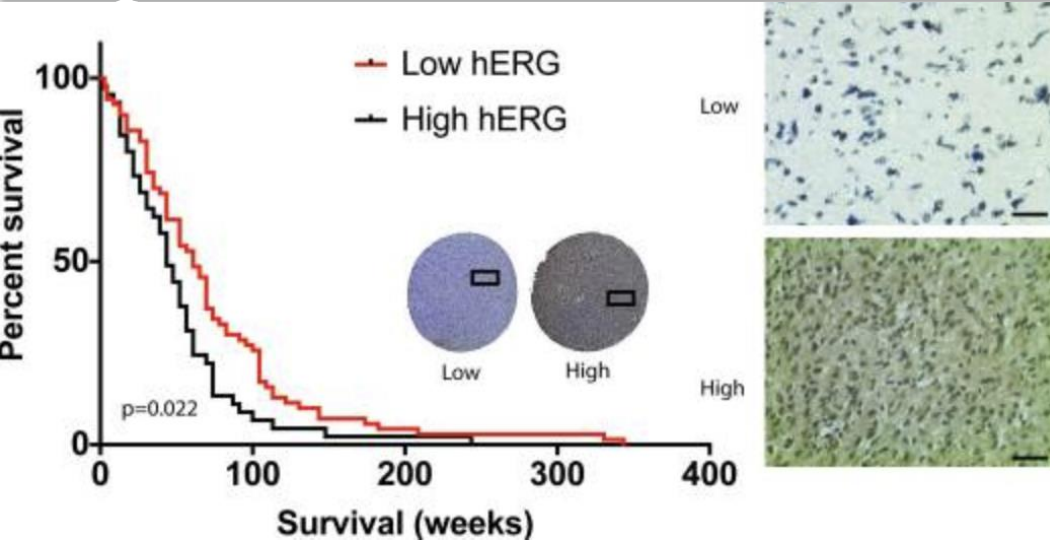
Human Ether-à-go-go Related Gene (hERG) voltage gated K⁺ channel

- Certain ion channels and transmembrane proteins have been reported to influence the progression of GBM and other cancers.
- The human Ether-à-go-go-Related Gene (hERG) is a voltage-dependent K⁺ channel (also found in cardiac cells) which is reported to be overexpressed in GBMs and lead to worse patient outcomes
- Elevated hERG levels have been linked to more aggressive mesenchymal GBM subtypes



- Member of the The *Ether-à-go-go* (*Eag*) gene family
- hERG1, hERG2, hERG 3 are found in the brain

hERG expression is correlated with GBM patient survival



- hERG is a potential glioblastoma survival marker
- FDA approved drugs that are non-cardiac toxic may be good targets for GBM therapy in patients with elevated hERG-expressing tumors.

Pointer et al. *CCR* 2017

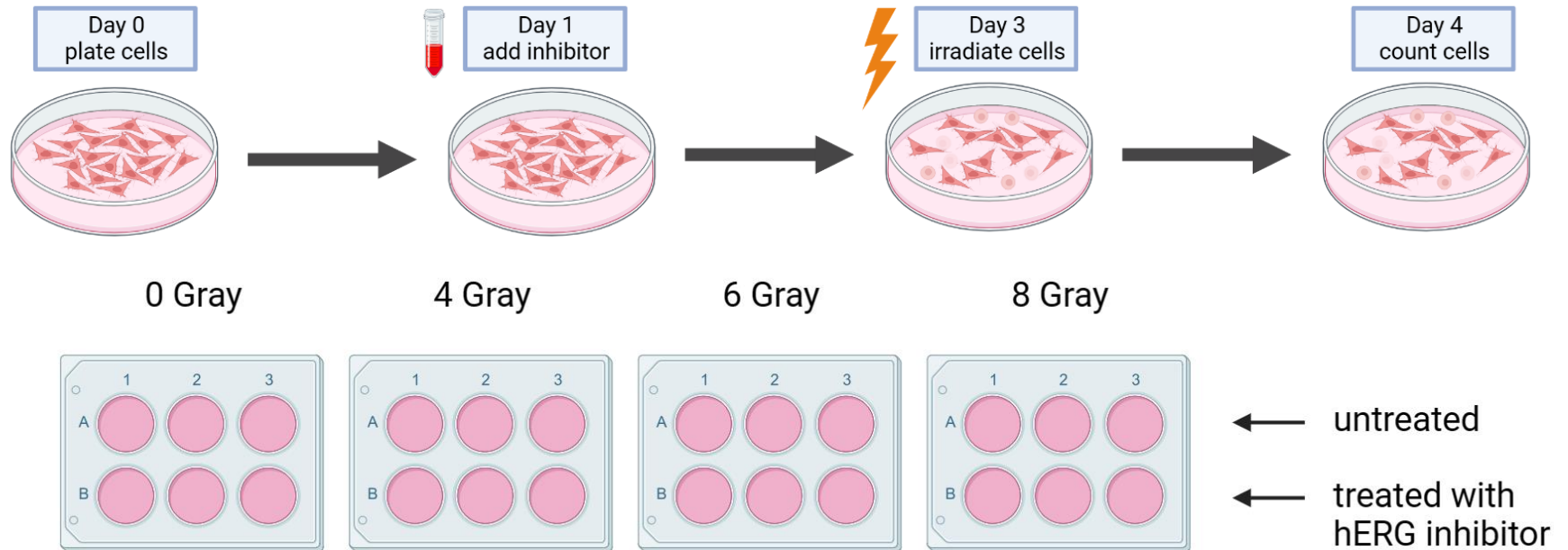
HYPOTHESIS AND AIM

- Many FDA drugs have secondary hERG inhibitor properties with the potential to be repurposed as a radiation sensitizer.
- These drugs cross the blood brain barrier, are not cardiac toxic, are in use at concentrations clinically for other purposes that are still at hERG inhibitory levels, and have low side effect profiles.

hERG elevated levels may lead to increased radiation resistance in glioblastoma cells

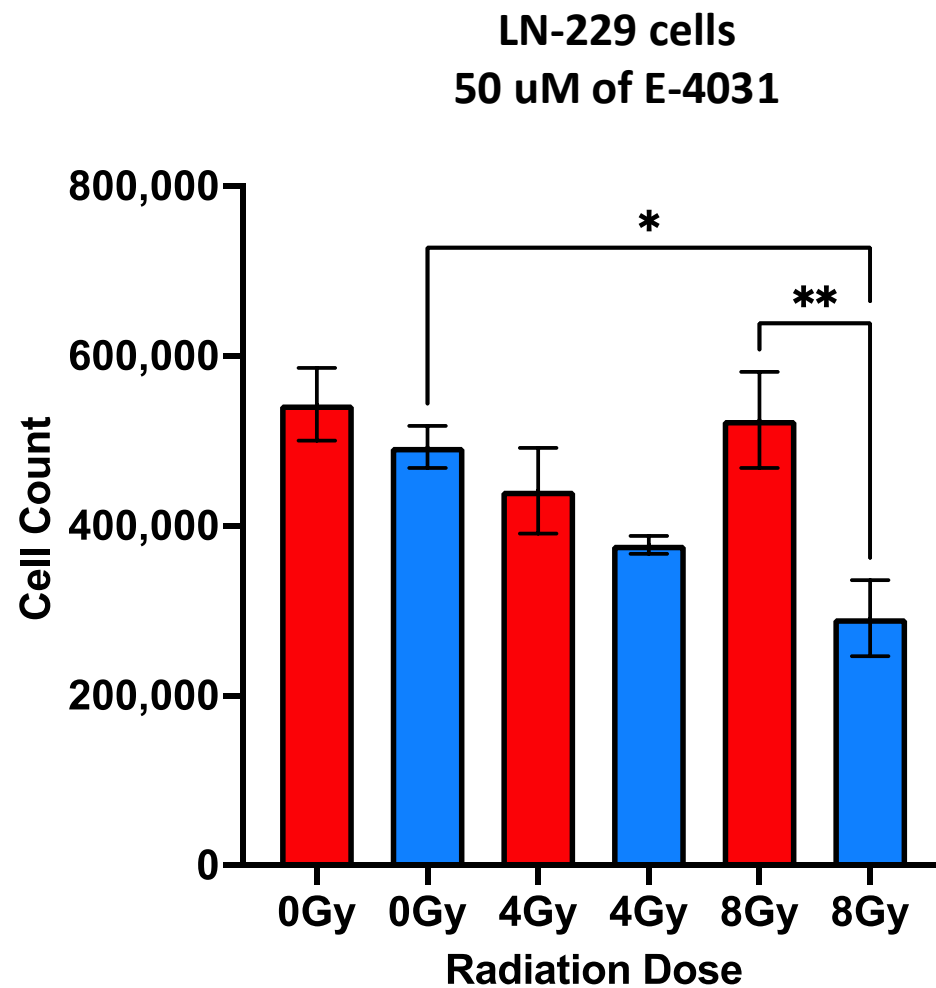
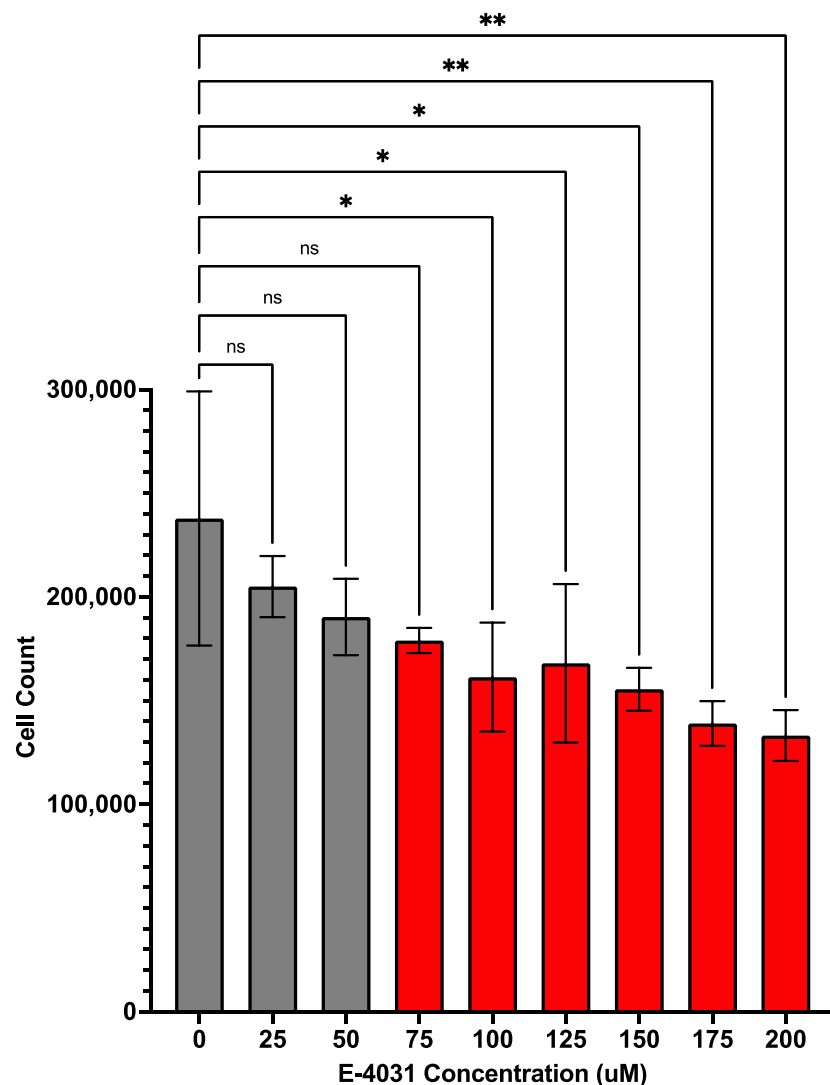
Determine whether hERG blockade will lead to increased radiation sensitization

Methods: Cell Viability Assay

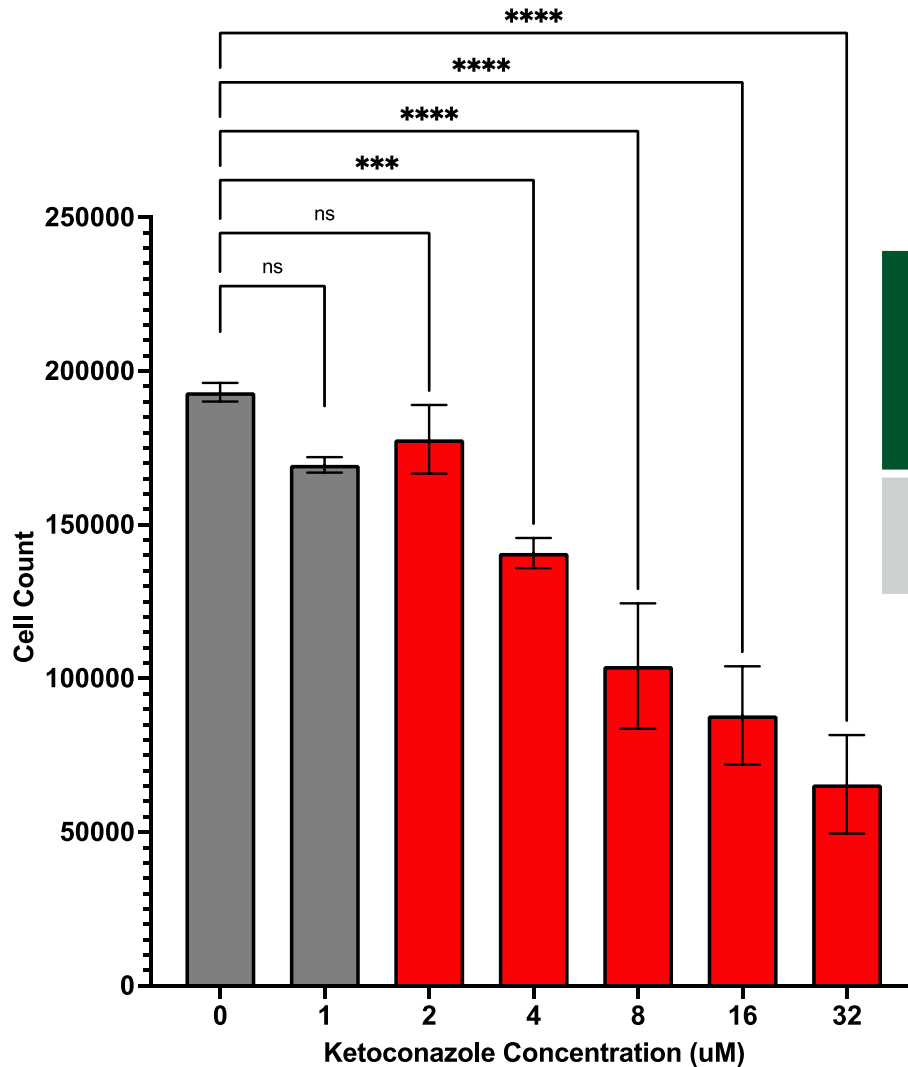


Courtesy of Elisa Bu Sha
Biorender

Selective hERG inhibitor, E-4031, in combination with radiation therapy synergistically causes a decrease in GBM cell viability



Ketoconazole Decreases GBM Cell Viability



Drug	hERG1 inhibitory IC50 (μM)	Therapeutic Serum Range used in clinic (μM)
Ketoconazole	1.9	13.2-32.0

Conclusions

- GBM patients have poor outcomes with the current standard of care
- hERG 1 blockade with a selective hERG inhibitor, E-4031, leads to radiation sensitization of GBM cells
- Ketoconazole, an FDA approved drug with hERG inhibitor properties, is able to decrease GBM cell viability.
- hERG 1 blockade may be a potential strategy for radiation sensitization in GBMs with repurposing of drugs that are already FDA approved and tested for hERG inhibition, as well as safety

Future Directions

- Create CRISPR/CAS9 mediated hERG knockout cell line in order to further investigate the mechanism behind hERG radiation resistance
- Investigate the role of radiation sensitization with more FDA approved hERG inhibitors

Drug	hERG IC50 (μM)	Therapeutic Serum Range (μM)
phenytoin*	100	39.6-118.9
fluoxetine *	3.1	0.29- 2.59
haloperidol	0.027	0.013-0.040
tamoxifen	1	0.41-1.9
amitriptyline	4.66	0.28-0.79
ketoconazole	1.9	13.2-32.0
* known to have higher brain concentrations		

LESSONS

BASIC SCIENCE RESEARCH

- There are different glioblastoma cells lines, and they have different doubling times.
- Techniques such as cell culture, cell count and use of the XRAD machine.

CLINICAL SHADOWING

- There are different subspecialties in RO
- The steps to get to treatment for patients involve treatment plans, simulations, contouring and the actual radiation treatment. Each treatment depends on the type of tumor, location and size.

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